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**Grounding and retrieving biomedical database content with formal ontologies**

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# Abstract

## **Motivation:** Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text Text.

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# 1 Introduction

Hypothesis generation in biomedical research depends on gathering data from publications and databases, such as UniProt (UniProt Consortium, 2014) or Ensembl (Cunningham *et al.*, 2014). The exploration of their content is performed manually or (partly) supported by retrieval tools, e.g. by STRING (Szklarczyk *et al.*, 2014), or BLAST (Altschul *et al.*, 1990). However, the interpretation of these results may be biased by the researchers' capabilities, by the sheer size and heterogeneity of the sources, or by technical limitations (Triplet and Butler, 2011).

Ontology-based data access (OBDA) (Poggi *et al.*, 2008) -related applications enhance data retrieval by ontologies, which serve as a query vocabulary, e.g. within SPARQL (Harris and Seaborne, 2013) endpoints. Other tools rely on machine learning to interpret databases according to an ontological background (Fanizzi *et al.*, 2008; Lehmann, 2009).

Such approaches are limited by the need for user intervention, e.g. the manual interpretation of the finally retrieved content, and the ontology population with data. Commonly, they represent all data entities as individuals (ABox elements), which entails high processing cost (Hustadt *et al.*, 2005).

The current situation is characterized by a continuous evolution of high-quality structured knowledge resources, whereas less progress can be seen regarding their usage, interoperability and ontological grounding. Thus, the interpretation of results is left to the users and influenced by implicit background assumptions that may vary between users.

We address this shortcoming by advocating a seamless integration of database and ontology content, underpinned by formal-ontological principles (Smith …), which enforce an univocal interpretation of the database content. We hypothesise and demonstrate that this enables more powerful queries, supported by machine reasoning. This "ontological grounding" is based on previous work on the formalization of tabular representations in scientific literature (Santana *et al.*, 2011) and models of structured clinical information (Martinez-Costa *et al.*, 2015).

Ontological grounding means to identify ontology-level content in databases, and to axiomatize it under an upper level ontology. It delivers a homogeneous representation of data, linked to (parts of) existing ontologies. Ontological grounding can be applied to enhance database curation by automated reasoning and may enable the validation of database content, using a simple and expressive query language (DL Query). DL Query uses the semantics and reasoning procedures of Description Logics (DL) (Baader *et al.*, 2007), which allow querying across

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several databases at the same time, thus decreasing the costs of database integration.

To this end, we will (i) analyse a subset of biomedical ontologies and databases; (ii) propose an ontology-based framework that makes explicit both database content and the domain entities denoted thereby; (iii) relate this solution to current workflows in which life science data and kno- wledge are acquired and processed; (iv) implement an example ontology from real data as an exemplar for data integration across ontologies and databases; (v) validate this example by demonstrating how querying beco- mes simpler and more user-friendly; (vi) perform an experiment to assess the scalability of the approach.

The biological use case is addressed Competency Questions (CQs) (Gruninger and Fox, 1994) as DL queries. They range from how data related to a specific metabolism overlap in biological databases for certain model organisms, to phenotypes from dysfunctional metabolism. Our examples make use of UniProt, NCBI Taxonomy (NCBI Resource Coordinators, 2015), Ensembl, GO (The Gene Ontology Consortium, 2014), ChEBI (Hastings *et al.*, 2013) and PR (Natale *et al.*, 2014), organized under the upper domain ontology BioTopLite (BTL2) (Schulz and Boeker, 2013).

# Background

## Formal ontologies

Formal ontologies are centred around classes. Together with a set of binary relations and logical operators in a logic-based language, e.g., DL, they constitute formal axioms. Axioms state what is universally true for all members of a class or a class-like expression. For instance, all nucleic acid molecules contain nucleotides, or all adenine molecules are nucleotide molecules. The construction of (formal) ontologies should obey principled criteria (Spear, 2006) and good practice guidelines (Schulz *et al.*, 2012). Important principles are (i) naming conventions (Schober *et al.*, 2009); (ii) mutually disjoint upper-level classes like *Process* or *Quality* as a fundamental ordering framework; and, (iii) a generally small set of canonical relations (Smith *et al.*, 2005),

We distinguish ontology content proper from both the notions of kno- wledge (Schulz and Jansen, 2013) and data. Regarding knowledge 1, assertions about what is frequently associated or only true by default can- not be straightforwardly expressed by formal ontologies. Regarding data, interpretation is often blurred by use-mention confusion, i.e. mixing data items with the things they denote. In databases, the interpretation of data elements is determined by the use cases embedded in the underlying schema. The distinction between what is a data element and what is its referent is often implicit. Formal ontologies should enforce this distinction: data items are instances of information content entities, whereas the things data items denote are manifold: individuals, classes, or even nothing\cite{schulz.icbo2011}.

## Interpreting databases with ontologies

Databases and less-principled domain ontologies leave the real nature of the entities as well as and the circumstances of denotation underspecified, assuming that this is intuitively known by the users and interpreted accordingly within the expected context of use. e.g. whether “Human” denotes an individual *Homo sapiens*, the class ‘*Homo sapiens*’, the quality of an object belonging to the taxon *Homo sapiens* (Schulz *et al.*, 2008), or a population of humans. In a similar vein, “Animal” could be interpreted as including the class ‘*Homo sapiens*’, in the context of biology or excluding it, e.g. in the context of Law. Such ambiguities underline the need to make these hidden assumptions explicit, such as by ontological grounding.

Content retrieval applications that use existing domain ontologies as vocabularies, like the ones derived from OBDA might benefit from this. As ODBA tools are not able to retrieve and generate new ontology content, the interpretation goes beyond what the user has specified as task-specific mappings between databases and ontologies. This requires that databases do not only use domain ontologies as standardized vocabularies, but that the meaning of their entire structure and content is described by ontology axioms and assertions. This is what we propose.

## Description Logics and OWL2

Description Logics (DLs) are representation languages used to formalise ontology content2. DL classifiers, like HermiT (Glimm *et al.*, 2014), find new subclass links, identify equivalent classes, and assure satisfiability, by spotting contradictory axioms. TBox expressions are class level axioms (e.g., “all chimps are primates”), whereas ABox contain assertions on individuals (e.g., “Washoo is a chimp”).

The Semantic Web Standard OWL2 (W3C, 2012) uses the DL lan- guage *SROIQ* (Horrocks *et al.*, 2006), with limited expressiveness but complete and finite reasoning. OWL2 supports classes, binary relations (called object properties), and individuals, together with related axioms and assertions. For instance, the OWL2 class ‘*Drosophila melanogaster*’ has all individual drosophila as members. As all individual drosophila are members of *Organism*, we can infer taxonomic subsumption: ‘*Drosophila melanogaster*’ forms a subclass of *Organism* iff all particular drosophila are equally members of *Organism*.

Such class statements are constructed by the combination of opera- tors specified in OWL2, viz. ‘and’ for conjunctions, ‘or’ for disjunctions,

such as ‘**has participant**’ or ‘**has part**’. Both top-level classes and canonic

relations are usually supplied by top-level ontologies, such as BFO (Spear, 2006), RO (Smith *et al.*, 2005), or BTL2.

1 In a broader sense, Cf. (Rector, 2008)

2 For DL syntax and semantics, Cf. (Baader *et al.*, 2007)

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‘some’ for existential restrictions, and ‘only’ for value restrictions, under the Manchester Syntax for OWL2 (Horridge and Patel-Schneider, 2009)3.

## Application background

For the use case, we use data and ontologies related to the metabo- lism of homocysteine (Hcy). Hcy is an amino acid, which plays a key role in vitamin and cofactor metabolism, neuronal metabolism, and in the biological oxidation of enzymes. Hcy is also involved in the metabolism of sulphur-based amino acids, where it can be converted into methionine or cysteine (Vitamin B6 dependent). When converted into methionine, the reaction depends in cobalamin (Vitamin B12) and requires 5-methyltetrahydrofolate (5-methyl-THF) (Selhub, 1999). The latter is result of the reduction of 5,10-methyl-THF via 5,10- methyl-THF reductase, an enzyme that regulates Hcy levels (Selhub, 1999). High levels of Hcy are reported to play a role in the pathogenesis of atherosclerosis (Muniz *et al.*, 2006), and of hepatic steatosis in hepatitis C infected subjects (Siqueira *et al.*, 2011). Many organisms host Hcy- related bioprocesses, e.g. *Mus musculus*, *Homo sapiens*, *Gallus gallus*, *Schizosaccharomyces pombe*, and *Oryza sativa*.

# Resources

## Biomedical Ontologies

* The **Gene Ontology** (GO) was created in 1998 to address biomedical information integration through standardization of terms for the anno- tation of DNA sequences and their respective characteristics. GO has become a crucial resource for functional genomics, as an ongoing col- laborative effort that delivers a controlled vocabulary underpinned by an ontology language. GO provides class hierarchies under ‘*Cellular component*’, ‘*Biological process*’, and ‘*Molecular function*’ (ontolo- gically better described as molecular activities or processes), together with the relations between them.
* **Chemical Entities of Biological Interest** (ChEBI) describes low- molecular-weight chemical entities for understanding and intervening in biological functioning. Each ChEBI entry denotes a chemical stru- cture in a graphical form, together with ontological axioms. The ontology is subdivided into ‘*Molecular structure*’ and ‘*biological role*’. Whereas the further represents the structure of small molecules and their constituents, the latter is used to classify molecules depending on their disposition of participating in biological processes.
* The **Protein Ontology** (PR) is held by the Pro- tein Information Resource (PIR), integrating several databases and responsible the cur- rent structure for the UniProt database. It represents modified forms, isoforms and protein complexes from living organisms and provides relations between them.
* **SNOMED CT** (Donnelly, 2006) is a large clinical terminology for human and veterinary medicine, containing formal definitions, which can be transformed into an OWL-EL ontology. SNOMED CT covers clinical findings and disorders, body parts, devices, drugs, substances, organisms and clinical procedures, among others.
* **BioTopLite 2** (BTL2) is a lightweight and redesigned version of Bio- Top, created in 2006 as an upper-domain ontological layer to enable the representation of general aspects of biology and medicine. BTL2 offers highly constrained classes, using a small set of relations. Classes like *Organism*, ‘*mono molecular entity*’, and ‘*body part*’ facilitate the alignment with other ontologies like GO, PR and ChEBI. BTL2 can be

3 In this work, classes are written in *italic*, binary relations (OWL object properties) in **bold** case.

aligned with most of BFO and RO. Available biomedical ontologies compliant with these two sources can easily be integrated with BTL2.

## Biological Databases

* The **Universal Protein Resource** (UniProt) was created in order to enable a quick understanding of the field of proteomics. It provi- des a comprehensive, open-access resource of protein sequences and functional information. UniProt is mainly composed by a Knowledge Base (UniProtKB), subdivided in SwissProt (manually curated) and TrEMBL (generated and maintained by automated tools). Other parts are databases for sequences, closely related protein sequences, protein information from fully sequenced organisms, and metagenomics.

Data from literature and available in UniProt are organized and stored according protein and gene names, function, catalytic activity, cofactors, pathway information, sub-cellular location, among others. UniProt embeds NCBI Taxonomy identifiers directly throughout its structure, as well as GO annotations (Huntley *et al.*, 2014), together with mappings to several biological databases including Ensembl.

* The **Ensembl** project was launched in 1999 in order to automatically annotate genomes and to integrate this data with other biological data sources, thus creating a freely available online source. Ensembl proces- ses and summarizes large-scale genomic data for chordates and model organisms. Its content is related to the annotation of gene and transcript locations, gene sequence evolution, genome evolution, sequence and structural variants and regulatory elements.
* The **NCBI Taxonomy** was derived from a project on the taxonomy of biological organisms that aimed at extracting sequences not avai- lable in dedicated databases from genomic literature. This coincided with the collection of data about taxonomic classifications. The goal of NCBI Taxonomy is to combine existent, distributed organism taxonomies into a single one that is included in NCBI GenBank.

# Methods

In the following, data acquisition and the methodology for converting database content into ontology axioms are described. Content and related files, such as spreadsheets, scripts, and ontology files are available in the project website [(http://www.cin.ufpe.br/˜inte](http://www.cin.ufpe.br/)grativo).

## Sampling

Data related to 21 organisms4, together with processes and by-products related to Hcy metabolism were retrieved from the UniProt website and Ensembl5. The ontologies GO, ChEBI and BTL2 were downloaded in OWL2 format6.

For the creation of a subset from UniProt and Ensembl, UniProt data were filtered by the string “homocysteine”, thus retrieving all Hcy-related data from UniProt/SwissProt+Trembl. From the obtained 212,156 records the ones with GO annotations, specified gene names and proteins descri- bed by Selhub (1999) were selected. From the resulting 1,716 records fragments, isoforms or homologue entries are excluded.

4 Giant panda, Bovine, white-tufted marmoset, dog, zebrafish, chicken, human, West Indian ocean coelacanth, African elephant, mouse, European domestic ferret, Nile tilapia, rabbit, chimpanzee, Sumatran orangutan, rat, Tasmanian devil, pig, Japanese pufferfish. Western clawed frog

5 UniProt: Release 2015\_04, Ensembl Release 79, NCBI Taxonomy 2015AA.

6 GO Revision 25527, ChEBI Release 127, BTL2 Release 8th march 2015, PR release 22nd may 2015

The resulting set includes the proteins Methionine synthase (MS), Methylenetetrahydrofolate reductase (MTHFR), Cystathionine beta- synthase (CBS), and Gamma-cystathionase (CSE). After removing records without Ensembl IDs, a final sample with 46 Hcy-related records is made available as a Microsoft Excel spreadsheet with the following tabular structure:

* + - One Protein (e.g. *CBS)*;
    - One Taxon (e.g. *Rattus norvegicus*);
    - One to many GO biological processes (e.g., *Blood vessel remodeling*)
    - One to many GO molecular functions (e.g., *Cystathionine beta- synthase activity*)
    - One to many GO cellular components (e.g., *Cytoplasm*)
    - Zero to many phenotypes (e.g., *Endocrine pancreas increased size*)

## Ontological grounding and ontology generation

The grounding process requires in-depth biology knowledge, insight into the way biological databases are populated, as well as ontology engineering skills, based on the understanding of upper level ontology principles and description logics. Aware that a straightforward, automatized “ontologization” of a database schema is not possible, the ontology engineer has to critically assess the pros and cons of competing modelling strategies. This must be performed in a way that correctly accounts for the underlying biological reality on the one hand, and that provides enough expressiveness to address the use cases (formulated as competency questions), on the other hand.

The workflow can be described as follows:

* Top-level classes and relations of the domain ontologies are ali- gned with the upper level ontology (cf. Fig. 1). Additional content relevant for a complete representation is added.
* Consistency of these alignments is assured by a DL reasoner.
* For performance optimization, modules of external ontologies (GO, ChEBI and PR) are created, with the classes referred to in the selected database content as signature, using the plug-in Ontology Modularity (Jiang et al., 2011), together with Protègè.
* Database objects are subjected to ontology-inspired scrutiny: while generally categorized as information entities, data objects have to be connected to their referents in the domain, for which it is decided whether they are individuals or classes.
* The interdependencies and relationships between the referents and/or their types are analysed, based on domain knowledge.
* The need for newly defined subclasses is assessed.
* Prototyping is done by manual creation of a small OWL file based on a limited number of database records. It is submitted to repeated satisfiability testing and discussions among experts for representational richness and adequacy, looking at computed entailments and results of typical queries.
* Numerous iterations are done, regarding choice of object properties, quantifiers, nesting of logical expressions, reference to implicit know- ledge. Whenever a decision leads to reasoning errors it is revised.
* Recurring structures are identified, which results in the abstraction of ontology patterns to be used for the whole database content.
* The sample ontology is translated into OWL XML format and manu- ally dissected in order to identify variable and fixed elements. All variable elements are identified by placeholders.
* Both database extract and ontology patterns with placeholders are represented as spreadsheets.
* The target ontology is generated by transforming database content with ontology patterns, using a customized script that takes spreadsheet content and generates OWL code using VBA scripts in MS Excel.

btl2:‘*particular*

*at some time*’

btl2:*disposition*

btl2:‘*Material object*’

so:‘*sequence feature*’

btl2:‘*Process*’

chebi:*role*

btl2:*compound*

go:*biological process*

go:*molecular function*

chebi:‘*chemical entity*’

btl2:‘*poly molecular composite entity*’

chebi:‘*molecular*

*entity*’

btl2:‘*structured biological entity*’

pr:*protein*

btl2:*organism*

go:*cellular*

*component*

**Fig. 1.** Alignment of GO, ChEBI and PR under BTL2. 1. One or more references to GO classes in UniProt annotations for GO classes, such as go:‘Biological process’ go:Methylation inclu- ded as annotation for ‘Methionine synthase’ in UniProt, as well as go:‘Cellular component’ and go:‘Molecular function’ classes;

2. Reference to Proteins from PR directly as protein names in UniProt;

3. Database IDs from Ensembl in UniProt, and vice-versa;

4. Organism names as described in NCBI Taxonomy inside Ensembl and UniProt;

5. Phenotypes according to Ensembl and included as a list of subclasses of BTL2 Situation, alinged with Clinical finding in SNOMED CT.

Figure 1 illustrates the final mapping structure of GO and ChEBI with BTL2.

## Methodology for CQ evaluation

The ontological content is evaluated by a set of competency questions (CQs). Formulated in English by the first author, a biologist, they are shaped according to how domain experts would query a biological database, and not how ontology engineers would interpret it, in order to be neutral regarding the internal structure of the ontology.

The translation of these CQs into DL queries relies on the correct identification of query components that denote relations, referents, and the way how domain entities are related to one another (cf. section 5.4.2.)

The following CQs were formulated:

1. Which kinds of biological processes related to Hcy can be found in mice?
2. Which are the proteins that exhibit ‘*methyltransferase activity*’?
3. Which are the kinds of biological processes in which proteins of the type ‘*cystationine gama lyase*’ participate, exhibiting ‘*carbon-sulfur lyase activity*’?
4. Which dysfunctional biological processes entail a risk of ‘*Atherosclerosis*’?
5. Which kinds of organisms are capable of performing *cysteine biosynthesis*?
6. Which proteins found in organisms of the kind ‘*Bos Taurus* have the capability of *methionine biosynthesis*?

CQs were selected to provide examples that explore entity types expres- sed in data, like phenotypes, proteins, molecules and biological processes from several organisms. To avoid biased judgements, the grounding pro- cess is assessed by means of description logics classification and retrieval of content from the axioms generated. This is possible as CQs are rendered as DL queries and submitted to the final ontology.

## Methodology for evaluation of scalability

Scalability is evaluated by artificially increasing the size of the ontology by the factors f \in {3, 10, 30, and 100}. This is done by programmatically creating new classes suffixed by i \in {1... f}. Tangledness of these experimental ontologies is guaranteed by random assignment of *i* in the axioms.

# Results

## Basic assumptions

The database content inspection was performed according to the following interpretation:

Each DB record implicitly introduces a series of defined subclasses of a biological process class. Each of these subclasses is defined by having proteins of a certain type as well as the small molecule Hcy as participants, occur within certain cell components, are parts of certain biological processes. In addition, only dysfunctional processes lead to the risk of developing the pathological phenotypes mentioned in the source.

Thus, the content of the biological databases under scrutiny is entirely expressed at class level. It makes the assumption that all these defined subclasses are nonempty, as otherwise there would not have been any experimental evidence manifested as a curated database entry. Additionally, we assume that no wrong data occur (data instances that do not have any referent in reality). This interpretation allows us to refrain from reasoning about individuals, which avoid known scaling problems.

Each record from UniProt and Ensembl is interpreted as unique; one or more similar experiments may have resulted in the population of a single DB record.

## Ontological Grounding

Table 1 shows a subset of the table created as a view from UniProt and Ensembl. We translate the content from Table 1 as an example Table 2 for interpretation. In particular, the ontological interpretation of data in Table 2 yields the following:

* There exist biological processes of the type *Bp* in organisms of the type

*O* that have the protein *P* and the small molecule *M* as participants;

* In each *Bp*, the protein *P* is capable of performing one or more molecular functions (processes) *Mf* ;
* *Bp* processesoccur in one or more types of cellular components *C*;
* There exist biological processes of the type *Bp* that are dysfunctio- nal and therefore bear the risks of causing one or more pathological phenotypes of the type *Ph*;
* All organisms of the type *O* have dispositions to be realized by *Bp* processes.
* All types of protein *P* in *O* are able to perform *Mf* processes;
* Proteins of class *P* are not organism specific. However, as the DB records refer to organism specific proteins we introduce subclasses *P\_sensu\_O* for each DB record (Protein *P* from Organism type*O*).
* Each *Bp* referred to by in a DB record may happen within the same cellular structure in several organisms *O*, including organism-specific proteins *P* and molecules *M*. However, each DB record denotes an exclusive occurrence of *Bp*. In this sense, each DB record represents specific subclasses of *Bp*, identified as *Bp\_in\_O\_with\_P\_and\_M*, generated as a combination of biological process, organism, protein and small molecule.
* The database structure leaves open in which cellular component *C* a given *Bp* subclass is located, when there is more than one entry in the cellular component field. For this reason, we generate union classes of the type *C*1 or *C*2 or …or *Cn* to which the process locations can be safely assigned.
* The DB structure is not explicit enough to connect a *Bp* subclass to a specific *Mf* process. Therefore in the definition of each *Bp* subclass the *Mf* processes are attached to the protein agent of that *Bp* subclass as possible realisations of the related disposition class (‘**is realized by**’ only *Mf* ) .
* If there are phenotype entries *Ph*, a new class of the type *Dysfunctional\_Bp\_in\_O\_with\_P\_and\_M* is generated for every *Bp\_in\_O\_with\_P\_and\_M*, and all phenotypes are referred to as being the realizations of risks.

## Ontology patterns

This analysis allowed us to identify ontology patterns. First, we present the axiomatic definitions of *P* (table 3), *Bp* (table 4) and *C* (table 5) .

Table 3. Defined Subclasses of proteins P.

*P* subclassOf pr:*Protein* ; *P\_sensu\_O* subclassOf *P*

*P\_sensu\_O* equivalentTo *P* and (‘is included’ in some *O*)

Table 3 shows how proteins of any type *P* within a single database record are introduced as defined subclasses of pr:*Protein*. The composed name concerning the protein of a specific organism *P\_sensu\_O* is a type of *P*.

Table 1. Uniprot and Ensembl table view.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Entry | Protein | Organism | GO (bp) | GO (mf) |  | GO (cc) | Ensembl ID | Ensembl Phenotype |
| F1MEW4  Q99707 | CBS  MS | *Bos taurus*  *Homo sapiens* | blood vessel remodeling; …  cobalamin meta- bolic process; … | cystathionine synthase acti  … cobalamin binding; … | *β*- vity | cytoplasm …  cytoplasm … | ENSBTAT00000000184; …  ENST00000366577; ENST00000535889 | No phenotype associated  Neural tube defect; Mega- loblastic anemia; … |

UniProt entries in the left, and Ensembl in the right. GO (bp) , GO (mf) and GO (cc) represents rows from UniProt that include annotations for GO classes ’*Biological process*’, ’*Molecular function*’ and ’*Cellular component*’ respectively. IDs from UniProt and Ensembl are used only for mapping purposes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2. Template table. |  | | | | | | | |
|  | # | *P* | *O* | *Bp* | *Mf* | *C* | *Ph* | *M* |
|  | *k* | *Pk* | *Ok* | *Bp*1 *. . . n* | *Mf*1 *. . . n* | *C*1 *. . . n* | *P h*1 *. . . n* | *M*1 *. . . n* |
|  | … | … | … | … | … | … | … | … |
|  | *l* | *Pl* | *Ol* | *Bp*1 *. . . n* | *Mf*1 *. . . n* | *C*1 *. . . n* | *P h*1 *. . . n* | *M*1 *. . . n* |
|  | … | … | … | … | … | … | … | … |
|  | *m* | *Pm* | *Om* | *Bp*1 *. . . n* | *Mf*1 *. . . n* | *C*1 *. . . n* | *P h*1 *. . . n* | *M*1 *. . . n* |

The symbol # represents record IDs; *P* proteins; *G* genes; *O* organisms; *Bp* biological processes; *Mf* molecular function; *C* cellular component; *Ph*

phenotype; and, *M* the associate molecules.

Table 4. Defined Subclasses of biological process Bp.

*Bp* subclassOf go:‘*biological\_process*’ *Bp\_in\_O\_with\_P\_and\_M* subclassOf *Bp Dysfunctional\_Bp\_in\_O\_with\_P\_and\_M* subclassOf

*Bp\_in\_O\_with\_P\_and\_M*

Biological processes *Bp* are subclasses of go:‘*Biological process*’, and the combination of a specific biological process of a record with the rela- ted organism, protein and small molecule(s) determines the creation of *Bp\_in\_O\_with\_P\_and\_M* as subclasses of *Bp*.

Cellular components of any type *C* (within a single record) are put as subclasses of go:’*cell\_component*’ (Table 5).

Table 5. Cellular component C union classes.

*C* subclassOf go:‘*Cell component*’

*C*1*\_or\_Cn* subclassOf go:‘*cell\_component*’

*C*1\_*or*\_*Cn* equivalentTo (*C*1 or *C*2 or …or *Cn*)

When a record includes more than one cellular component, union classes type *C*1 or *C*2 or …or *Cn* are created under go:*cell\_component*. This is due to the fact that the DB structure is not explicit enough to connect specific cell components to specific process subclasses.

Table 6 shows the axioms for *Bp\_in\_O\_with\_P\_and\_M* classes.

Table 6. Bp\_in\_O\_with\_P\_and\_M.

*Bp\_in\_O\_with\_P\_and\_M* equivalentTo *Bp*

and (‘**has participant**’ some *M*) and (‘**has participant**’ some (*P* and

(‘**is bearer of**’ some (btl2:*Function* and (‘**is realization of**’ only *Mf* )))

and (‘**is included in**’ some *C*1 or *C*2 or …or *Cn*) and (‘**is included in**’ some *O*)

Table 7. Dysfunctional phenotypes of Bp\_in\_O\_with\_P\_and\_M.

*Dysfunctional\_Bp\_in\_O\_with\_P\_and\_M* equivalentTo

*Bp\_in\_O\_with\_P\_and\_M*

and (‘**is bearer of**’ some ‘*Dysfunctional Quality*’) *Dysfunctional\_Bp\_in\_O\_with\_P\_and\_M* subClassOf

*Bp\_in\_O\_with\_P\_and\_M*

and (‘**is realization of**’ only (*Risk* and (**causes** some *Ph*)))

*Dysfunctional\_Bp\_in\_O\_with\_P\_and\_M* are processes that bear the quality of being dysfunctional. They are realizations of a risk (a sort of disposition) of causing the dysfunctional phenotype stated in the DB.

Following, the axioms required to represent *P\_sensu\_O* (Table 8), i.e. the protein type of a specific organism from a DB record.

Table 8. Subclasses created for the organism specific protein (P\_sensu\_O) classes in database records

*P\_sensu\_O* equivalentTo *P* and (‘**is included in**’ some *O*)

*P\_sensu\_O* subClassOf *P* and (‘**is bearer of**’ some (*Function* and (‘**has realization**’ only *Mf* )))

Definitions that follow the pattern from Table 8 describe organism- specific protein molecule classes. In addition, the *Mf* processes specified in the DB records are added.

The last axiom required is about organisms as bearers of dispositions related to performing biological processes (Table 9) .

Table 9. Axioms generated for organisms O in database records

*O* subClassOf btl2:*Organism* and

(‘**is bearer of**’ some (*Disposition* and ‘**has realization**’ only *Bp*)))

Axioms for *Bp\_in\_O\_with\_P\_and\_M* (Table 6) describe that a bio- logical process from a single record has as participants one or more small molecules; the process is included in the combination of one or more cel- lular components; included in a specific organism; and, the protein from the record is a participant in the process, and bears some function to perform *Mf* processes.

Some *Bp\_in\_O\_with\_P\_and\_M* processes are dysfunctional and then bear the risk of pathological phenotypes (represented as SNOMED CT findings, ontologically btl2:situations).

Table 9 attaches dispositions realized by specific biological processes to organisms.

## Evaluating the content generated

The analysis of the content of database entries has resulted in a set of OWL T-Box axioms for each database record as specified above. We recall two basic assumptions made, *viz.* (i) non-emptiness of classes: i.e. each of the newly defined classed corresponds to at least one fact described

in literature, and (ii) the veracity of database entries, i.e. each informa- tion is considered a statement of truth. Given these boundary conditions, evaluation of the generated TBoxes will address the aspects: (i) logical satisfiability when importing all constraints from the upper-level-ontology BTL2; (ii) adequacy (correctness and completeness) of entailments against CQs; and, (iii) computational performance.

### Evaluation of Competency Questions (QCs)

In the following, each competency question is translated into a DL query. The result is analysed and discussed.

*CQ1*  (cf. Table 10): *Which kinds of biological process are included in organisms of a specific type of Mus musculus?* This query is intended to retrieve all biological process classes that take place in organisms.

Table 10. Competency Question #1 in DL

‘*Biological process*’ and (‘**is included in**’ some ‘*Mus musculus*’)

x classes (including ancestors) are retrieved. After filtering out the system-defined subclasses we obtain: *‘amino acid betaine catabolic process', 'blood vessel remodeling' …*

These results are expected as they match the content represented in data.. Here we see how a query on potentialities can be expressed as a simple DL query.

*CQ2:* (cf. Table 11). *Which are the proteins that are able to perform certain molecu- lar functions of type ‘methyltransferase activity’?* This query is meant to retrieve classes of proteins that are able to perform certain *mf* processes. It is important to highlight that some proteins are capable to act in a specific way, like polymorphisms in gene MS leads to methionine synthase deficiency, which leads to higher homocysteine levels together with dysfunctional phenotypes in humans and mice.

Table 11. Competency Question #2 in DL

*protein* and (‘**is bearer of**’ some *function* and

(‘**has realization**’ only ‘*methyltransferase activity*’))

Using DL query and reasoning, we obtain the following results:

* Results:
  + ‘*Betaine homocysteine S-methyltransferase 1 sensu Homo sapiens*’;
  + ‘*Methionine synthase sensu Mus musculus*’;
  + and 7 more classes.

These are the proteins able to perform for the ‘*methyltransferase activity*’ molecular function.

*CQ3: Which are the kinds of biological processes in which a specific protein of type ‘Cystationine gama lyase’ participates, and has the function of performing molecular activities of type ‘carbon-sulfur lyase activity’?* This query is related to the identification of biological processes (e.g. reactions) that involve a specific protein, a protein that should be able to performing this reaction. The relevance of this query is related to the capability of retrieving specific biological processes by means of proteins from specific reactions.

CQ3 is available below (table 12)

Table 12. Competency Question #3 in DL

‘*biological\_process*’ and

‘**has participant**’ some (‘*Cystationine gama lyase*’ and

(‘**is bearer of**’ some (*Function* and (‘**has realization**’ only ‘*carbon-sulfur lyase activity*’)))))

x classes (including ancestors) are retrieved, of which the following are displayed after filtering

‘cellular nitrogen compound metabolic process' , ‘cysteine biosynthetic process' …

*CQ4* (cf. Table 13)*: Which are the kinds of biological processes that entail some risk of causing a specific dysfunctional state of ‘Atherosclerosis’?* This query retrieves biological processes that entail the risk of developing a dysfunctional phenotype. This query is relevant in the sense whether it enables the identification of any abnormal situations regarding a specific process from an organism.

Table 13 (Table 14). Competency Question #4 in DL

‘*biological\_process*’ and (‘**is realization of**’ only (*Risk* and (**causes** some ‘*Atherosclerosis*’)))

x classes (including ancestors) are retrieved, of which the following are displayed after filtering: *‘Dysfunctional homocysteine metabolic process', ‘Dysfunctional response to interleukin 1' …*

*CQ5: Which kinds of organisms are capable of performing a specific bio- logical process of type of ‘Cysteine biosynthetic process’?* This query retrieves organisms that are capable of performing specific biological pro- cesses. This query is relevant because not all biological processes for organisms are fully described. Organisms from different species that include for which the same proteins under the same conditions are described may not include similar processes.

Table 14. Competency Question #5 in DL

*Organism* and (‘**is bearer of**’ some (*Disposition* and

(‘**has realization**’ only *‘Cysteine biosynthetic process*’)))

* + The following organism classes were retrieved: ‘*Homo sapiens*’; ‘*Mus musculus*’;…

*CQ6 (*Table 15): *Which are the proteins that are found in organisms of the kind ‘Bos taurus, which bear the capability to perform a specific biological process of the kind ‘methionine biosynthetic process’?* The aim of this query is to retrieve specific proteins that are related to the process ‘*methinine biosynthetic process*’, when performed by a organism of the type ‘*Bos taurus*’. In other words, we are able to identify specific proteins by means of organisms and biological processes among the content embedded in databases.

Table 15. Competency Question #6. in DL

*protein* and (‘**is included in**’ some (‘*Bos taurus*’ and

(‘**is bearer of**’ some (*disposition* and (‘**has realization**’ only

‘*methionine biosynthetic process*’)))))

x classes (including ancestors) are retrieved, of which the following are displayed after filtering: ‘Betaine homocysteine S-methyltransferase 1", ‘Cystathionine beta synthase' … COMPLETE

### Computational performance

Data, ontologies and queries were manipulated with an Windows 10 x64 Intel-based core i7 4510U with 8Gbyte of RAM. The raw ontology presents expressivity *ALC* and took half a second for classification and consistency checking. The inclusion of the GO, ChEBI and PR modules aligned with BTL2 raised the expressivity to *SRI* and resulted in 1.9 hours classification and consistency checking time.

The ontology with modules includes 3,284 subclass axioms, 980 equivalence axioms, 973 hidden general class inclusions, and 1,721 classes. However, for querying purposes, reasoning complexity takes much less time (all CQ1-CQ6) to be computed, in comparison with the overall ontology classification procedure. Even with the increase in computational complexity, CQ2 and CQ5 take few seconds to be computed.

# Discussion

A problem our work addresses is the formal interpretation of biological database content to enable content retrieval using a richer query paradigm. All queries target DL Tboxes, thus avoiding the import and inclusion of individuals. Reasoning is finite and complete, in contrast to the costs of rich TBoxes together with populated Aboxes (Motik and Sattler, 2006). The interpretation supports the notion of representing the content according to the classes the individuals are member, as observed in biological experiments.

The fact that typical queries target possibilities “*Are members of the class A able to do B?*” is addressed by two mechanisms. Firstly, the inclusion of dispositions as first-class entities in our ontology, and secondly

the definition of specific subclasses. The latter case, however, requires the assumption that all of these classes are populated. In this sense, the que- stion “*Are members of the class A able to do B?*” is therefore translated into the question “*Does A have a subclass A’ all members of which actually do B?*”, to highlight the existence of classes, and not its direct assertion.

Interpreting database content under an ontological perspective has been a topic of research interest. Fanizzi *et al.* (2008) present a tool called DL- FOIL, which relies on refinement operators for class-learning. In DL-FOIL grounding is presented as learning by search of class definitions in an indu- ced search space. A limitation of DL-FOIL is the treatment of individuals that do not belong to a specific class, as well as the incompleteness of the refinement operator.

The DL-Learner system (Lehmann, 2009) is grounded on the requi- rement for schema acquisition methods, as they intend to address the problem with class learning techniques. DL-Learner is designed to find logical explanations for individuals inside the ontology. It is limited by the fact that positive and negative examples must be provided, and individu- als must be included directly in the ontology. As previously mentioned, querying axiomatized and populated ontologies is costly.

Interpreting data and grounding it as ontology axioms seems as a suita- ble solution to boost interoperability with the support of formal ontologies. However, the usage of principled ontologies as guidance for interpreting data is quite limited. Earlier, we described how the content of tables from scientific publications can be interpreted using formal ontologies under a rigid upper level, also using competency questions for evaluation (Santana *et al.*, 2011).

An improvement of our work could be the possibility of using more expressive power to retrieve generalizable content by means of DL Query. The retrieval of OBDA-based approaches, like SPARQL endpoints fairly supports reasoning that goes beyond what is available in current relatio- nal queries (Angles and Gutierrez, 2008). Our approach allows evaluating databases from the ontological level, e.g. computing class-subclass relations, consistency checking and subsumption. This reduces the need to manually filter/interpret data, without compromising the capability to be queried with SPARQL endpoints.

In this work, we re-affirm and demonstrate the power embedded in formal ontologies to represent database content. We model real data with the support of formal ontologies queries that requires reasoning at some extent, and exempt the user to know specific domain details to optimize domain query, like when creating relational or SPARQL queries.

For instance, to retrieve a protein that has methylation capability, with relational or SPARQL (without ontological treatments), the user must create joins and filters to gather content from different tables/filters. With DL query, we only need to define how the process behaves and leave the querying and computing complexity to the machine. One may argue that this approach generates more complexity to domain representations. However, this complexity is restricted to the representational level, and it is, at some extent, already covered by most formal biomedical ontologies.

The complexity – in the sense of manual creation of ontology patterns, however, appears necessary in order to produce a precise, ontology-based picture of what a database really represents, and how the informal database-ontology links are to be interpreted. The solution completely refrains from representing the denoting entities (data instances), setting the full focus on the denotations, hence its fulfils its goals without ABox reasoning.

Current solutions to acquire and process life science data have mainly focused on the analysis of networks, pathways, and sequences. Recent work has been concerned with the functional analysis of data, mostly limited to syntactic approaches, without sufficiently analysing the partly implicit meaning under the surface of data structures.

Several limitations need to be highlighted:

* Considerable scaling problems issues could be demonstrated when increasing the size of data. This can partially be mitigated by narrowing down the database content of interest, such as done in this example, where the content was filtered by one chemical entity, viz. Hcy.
* Another strategy for addressing computational issues would be to decrease the ontology expressiveness. The ontology patterns presented in this paper used disjunctions and value restrictions, both of which are not supported by the computationally ideal OWL EL profile. (to continue)

and ontologies. Other limitation is the understanding of the ontological representation from a usability point of view. The description of the formal aspects entails a deeper understanding of the ontology(ies) used, which is not required when creating database schema or informal representation.

Further investigations are required to address the impact that database updates may generate. Database updates may generate modification in the schema level that can lead to adaptations on the interpretation procedure, such as table joins or the obsolescence of certain content. We are cur- rently developing a system to support the interpretation procedure, which would minimize the deep ontological understanding required by current approach, and address the inherent awareness of data interpretation.

# Conclusion

We presented an ontology engineering framework that supports interpreta- tion of biological data, from different sources, using a highly constrained upper-level ontology, (BTL2), to which GO, PR and ChEBI were aligned. The ontology analysis of the content of biological databases yielded a set of ontology patterns, which were used to translate databases’ content into formal ontologies. The resultant ontological content was presented to formal scrutiny with DL queries, answered only by means of reasoning.

As we exemplified our framework under the biological domain, it can be ported to other domains that include highly constrained and formalized ontologies. For instance, Prestes *et al.* (2013) described an upper-domain ontology based on IEEE standards for representing intelli- gent agent systems knowledge bases, following DOLCE (Gangemi *et al.*, 2002) and SUMO (Pease *et al.*, 2002).

The ontology derivate we produce focus on TBox reasoning rather than the analysis of data itself. Following this, a databased grounded under a formal ontology might enable the identification of representa- tional flaws under real world situations, opposite to application-driven databases. As database is extensive by nature, its organization under real world settlements certainly would be improved when accompanied by formal ontologies. Additionally, it may enable further integration capabi- lities by means of automated evaluation using reasoning, e.g. without any dependence in user support.

According to our findings, this is possible because we interpret the entries in biological databases in ways that derive generalizable statements. These are expected to reveal scientific laws and can be ascribed to all indi- viduals that are members of a given class as well as database records. Reasoning can then be restricted to a TBox level, thus avoiding high pro- cessing cost that occurs when populating highly axiomatised TBoxes with individuals.

The feasibility of the approach could be demonstrated using com- pete- ncy questions formulated as DL queries. We query the data ontologically, without requiring any additional database processing. If the data interpre- tation is ontologically sound, by inheritance all data may be considered sound in a real world use case.

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